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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,576	10/17/2005	Mitsuharu Hirai	TOYA114.008APC	4658

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EXAMINER	
STAPLES, MARK	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
09/30/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/553,576	HIRAI, MITSUHARU	
	Examiner	Art Unit	
	Mark Staples	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08/27/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/24/2008 has been entered.

2. Applicant's amendment of claim 18 in the paper filed on 07/25/2008 is acknowledged.

Claims 18-21 are pending and at issue.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejections that are Withdrawn

Claim Rejections Withdrawn - 35 USC § 103(a)

3. The rejection of claims 18-21 under 35 U.S.C. 103(a) as being unpatentable over Critchley (19.09.2002) and Buck et al. (1999); as evidenced by Froguel et al. (1993) and by Howell et al. (1999) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection which are necessitated by claim amendment.

New Rejections Necessitated by Amendment

New Claim Rejections - 35 USC § 103(a)

4. Claims 18-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Critchley (19.09.2002, previously cited), Buck et al. (1999, previously cited), and Mackay et al. (March 15, 2002); as evidenced by Froguel et al. (1993, previously cited) and by Howell et al. (1999, previously cited).

Regarding claim 18, Critchley teaches methods for detecting a mutation comprising:

performing a melting curve analysis for a nucleic acid having a single nucleotide polymorphism site by using a nucleic acid probe labeled with a fluorescent dye and measuring fluorescence of the fluorescent dye (see the method of "dynamic allele specific hybridization, DASH, on p. 16, 2nd paragraph and its more complete description in the article titled "Dynamic allele-specific hybridization" by Howell et al.), and detecting the mutation on the basis of the result of the melting curve analysis, wherein the single nucleotide polymorphism is a mutation at the 3243rd position in a mitochondrial DNA (throughout the entire publication, especially the 2nd paragraph on p. 4 and claims 6, 28, 29 and 34).

Further regarding claim 18, Critchley teaches probes (see Abstract and see 1st full paragraph on p. 4) and teaches a sequence of 480 base comprising SEQ ID NOs: 21 and 22 (see sequence 13 on p. 9 of the sequence listings). There are 100% matches of SEQ ID NOs: 21 and 22 in this sequence as given in Table 1 below.

Table 1

(represented for ease of review)

100% Sequence Matches to SEQ ID NOs. 21 and 22

```
SEQ ID NO: 21          1 GGGCCCTGCCATCTTAAC 18
                         ||||||||||||||||||
Critchley's seq. 13  247 GGGCCCTGCCATCTTAAC 230  (reverse complement)


SEQ ID NO: 22          1 GGCCCTGCCATCTTAAC 17
                         |||||||||||||||||
Critchley's seq. 13  246 GGCCCTGCCATCTTAAC 230  (reverse complement)
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Regarding claim 18, Critchley does not specifically teach sequences consisting of SEQ ID NO: 21 or SEQ ID NO: 22 and does not specifically teach a nucleic acid probe having a 3' terminal cytosine labeled with a fluorophore.

Regarding claim 19, Critchley teaches wherein a region containing the single nucleotide polymorphism site in a nucleic acid contained in a sample is amplified to obtain the nucleic acid showing the single nucleotide polymorphism (see the method of DASH on p. 16, 2nd paragraph and its more complete description in the article titled "Dynamic allele-specific hybridization" by Howell et al.

Regarding claim 20, Critchley teaches wherein the amplification is performed by a method using a DNA polymerase (see 1st full paragraph on p. 24 and as referenced there to the PCR methods of Froguel et al. (1993) *N Engl J Med* 328:697 who give PCR methods using a DNA polymerase, see title of reference no. 15 there).

Regarding claim 21, Critchley teaches wherein the amplification is performed in the presence of a nucleic acid probe (see the method of DASH, on p. 16, 2nd paragraph

and its more complete description in the article titled “Dynamic allele-specific hybridization” by Howell et al.).

Claim 18 is rejected for SEQ ID NOs: 21 and 22, as described following. With regard to Claim 18, Critchley disclose probes to sequence 13. Critchley does not specifically teach sequences consisting of SEQ ID NO: 21 or SEQ ID NO: 22. It is noted that the instant probe sites of SEQ ID NOs: 21 and 22 are contained within the sequence disclosed by Critchley, as given in Table 1 above.

The above described references do not specifically disclose the identical probe sequences of SEQ ID NOs: 21 and 22 used in the claimed invention.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed probes simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for probes of the mutation at the 3243rd position in a mitochrondrial DNA and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the

claimed probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al (1999) expressly provides evidence of the equivalence of primers/probes. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer/probe would have a reasonable expectation of success.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Critchley by using any number of probes to the sequence disclosed by Critchley as suggested by Buck et al.

with a reasonable expectation of success. The motivation to do so is provided by Buck et al. who teach that a multitude of primers/probes to a given sequence give excellent results (entire article, especially the *Discussion* section). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Claim 18, reciting a nucleic acid probe having a 3' terminal cysotine labeled with a fluorophore, is rejected as follows.

Regarding claim 18, Critchley teaches probes having a 3' terminal cytosine as in sequences of SEQ ID NOs: 15, 18, 19, and 23 but does not specifically teach a nucleic acid probe having a 3' terminal cytosine labeled with a fluorophore.

Regarding claim 18, Mackay et al. teach oligoprobes that are 3' terminally labeled with a fluorphore which is FITC (see 2nd sentence under the section *Linear oligoprobes* on p. 1294) and teach that a 3' terminal cytosine is preferably labeled (see 4th sentence of 2nd paragraph on p. 1296).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the 3' terminal cytosine probes of Critchley by labeling the cytosine with a fluorophore as suggested by Mackay et al. with a reasonable expectation of success. The motivation to do so is provided by Mackay et al. who teach:

> "The probe was designed so that the fluorophore was located on a terminal cytosine and was quenched by proximity with a complementary guanine. The assay demonstrated that quenching varies linearly with the concentration of template across a defined concentration range. The commonly used fluorophore FITC is inherently quenched by deoxyguanosine nucleotides. The level of quenching can be increased if more guanines are present or a single guanine is

> located in the first overhang position, 1 nt beyond the fluorophore-labelled terminus of the probe. This approach to amplicon detection is easier to design than fluorogenic oligoprobes, simpler to synthesise and use in real-time PCR and does not require a DNA polymerase with nuclease activity" (see the last half of the 2nd paragraph on p. 1296)

Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

5. No claim is free of the prior art.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples
/M. S./
Examiner, Art Unit 1637
September 24, 2008

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637